REMARKS

Applicants noted with appreciation that the rejection of claims 31 and 58 under 35 U.S.C. §112, second paragraph and claims 31-35, 40-42 and 51 under 35 U.S.C. 103(a) has been withdrawn.

Claims 31-35, 40-42, 51, 58-62, 67-69, 78 and 97-99 were pending.

Claims 31, 32, 51, 97 and 99 have been amended. Claims 58-62, 67-69 and 78 have been cancelled without prejudice. Upon entry of these amendments, claims 31-35, 40-42, 51 and 97-99 are pending and under consideration.

I. CLAIMS AMENDMENTS

Claim 31 has been amended to delete the reference to non-elected subject matter such as "myosin heavy chain promoter" and "viral strain", as requested by the Examiner.

Claim 32 has been amended to delete the reference to non-elected subject matter such as "viral vector", as requested by the Examiner.

Claim 51 has been amended to recite an alpha-galactosidase gene. Support for this amendment can be found, for example, on page 6, lines 12-14 of the instant specification.

Claims 97 and 99 have been amended to correct dependency.

Therefore, these amendments do not introduce new matter. Accordingly, entry thereof is respectfully requested.

II. CLAIM OBJECTIONS

Claims 31-35, 40-42, 51, 58-62, 67-69, 78 and 97-99 are objected to as comprising non-elected subject matter.

Applicants have amended claims 31 and 32 to delete the reference to "myosin heavy chain promoter", "viral strain" and "viral vector". Therefore, amended claims 31 and 32 recite the elected subject matter. Claims 58-62, 67-69 and 78 have been cancelled rendering the objection moot with respect to these claims. Claims 33-35, 40-42, 51 and 97-99 depend upon amended claim 31. Accordingly, it is respectfully requested to withdraw the objection.

III. REJECTION UNDER 35 U.S.C. §112, 1st PARAGRAPH, WRITTEN DESCRIPTION

Claims 58-62, 67-69, 78, 97 and 98 are rejected under 35 U.S.C. §112, first paragraph,

as allegedly failing to comply with the written description requirement as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner is of the opinion that the method of treatment of alpha-galactosidase A deficiency, wherein the treatment does not comprise a blood coagulation factor, is not supported by the disclosure.

Without acquiescing in the rejection and in order to expedite prosecution, Applicants have cancelled claims 58-62, 67-69 and 78. Therefore, the rejection is moot with respect to these claims. Amended claim 97 depends upon amended claim 31, and claim 98 depends upon claim 97. Therefore, it is respectfully requested to withdraw the rejection.

Claims 31-35, 40-42, 51, 58-62, 67-69, 78 and 97-99 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner alleges that the claims broadly encompass a wide variety of metabolic disorders or conditions related to an alpha-galactosidase A deficiency and are not limited to ameliorating of the symptoms associated with an alpha-galactosidase A deficiency (Office Action, page 11). This rejection is traversed. Reconsideration is respectfully requested.

Applicants respectfully submit that the instant claims are drawn to a method of treating the underlying cause of an alpha-galactosidase A deficiency and not the symptoms of the disease. The underlying cause being a defect in alpha-galactosidase A gene resulting in deficiency of production of the corresponding enzyme.

It is respectfully submitted that the instant specification provides an extensive disclosure of all of the elements of the claimed methods. The compositions to be used in accordance with the claimed methods are fully disclosed in the instant specification, including the expression cassette, the myosin enhancer, the promoters, the polynucleotide sequences of interest and the vectors (see, *e.g.*, pages 3-7 of the specification).

Further, the specification provides an ample description of how the compositions of the invention can be used by way of working examples. In particular, the examples demonstrate the effect of muscle-specific regulatory elements on the expression of human α-galactosidase (see, *e.g.*, Table 1 on page 12 of the specification) and the enhanced

expression of the human α-galactosidase in the culture medium of the pX3F-, pX4F- or pX7F-transfected myoblasts (see, *e.g.*, page 13, line 16 through page 14, line 7 of the specification). It is noteworthy that these experiments were the first report in which a correctly glycosylated form of human α-galactosidase was expressed and secreted from differentiated muscle cells.

As all the essential elements of the claimed invention are adequately described in the instant specification, we believe that the written description requirement is satisfied. Claims 58-62, 67-69 and 78 are cancelled rendering the rejection moot with respect to these claims

The Examiner further alleges that as the specification provides no guidance as to what structure/function of a protein is envisioned to be used to treat the wide variety of symptoms associated with alpha-galactosidase A deficiency using heterologous genes, the claims do not satisfy the written description requirement (Office Action, page 11). Reconsideration is respectfully requested in view of the amendment of claim 51.

Applicants would like to reiterate that the instant claims are drawn to a method of treating the underlying cause of an alpha-galactosidase A deficiency and not the symptoms of the disease. As such, the amended claim 51, reciting a polynucleotide sequence comprising an alpha-galactosidase A gene, is fully supported by the disclosure that teaches that alpha-galactosidase A can be used to treat Fabry disease (for example, see page 6, lines 12-14). Accordingly, the claimed method is adequately described in the specification. As such, claims 31-35, 40-42, 51 and 97-99 satisfy the written description requirement. Claims 58-62, 67-69 and 78 are cancelled rendering the rejection moot with respect to these claims.

Therefore, it is respectfully requested that the rejection under U.S.C. 112, first paragraph, written description, be withdrawn.

IV. REJECTION UNDER 35 U.S.C. §112, 1st PARAGRAPH, ENABLEMENT

Claims 31-35, 40-42, 51, 58-62, 67-69, 78 and 97-99 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleges that the disclosure does not provide support that the claimed invention was enabled at the time of filing. Careful consideration has been given to the grounds for rejection. Reconsideration is respectfully requested in view of the discussion provided below.

A claim is enabled if one skilled in the art, guided by Applicant's disclosure, can make

and use the claimed invention without undue experimentation. *See, In re Wands* 8USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is not undue. *See, In re Angstadt*, 190USPQ 214, 219 (C.C.P.A. 1976).

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands* 8USPQ2d 1400, 1404. They include (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art; (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. Each of these factors in light of the instant specification is discussed below.

1) *Quantity of Necessary Experimentation*

Applicants respectfully submit that the instant specification provides an ample disclosure of all the elements of the claimed method. The compositions to be used in accordance with the claimed method are fully disclosed by the instant specification, including the expression cassette, the myosin enhancer, the promoters, the polynucleotide sequences of interest and the vectors (see, *e.g.*, pages 3-7 of the specification). Therefore, a skilled artisan based on the instant disclosure would be able to make and use the invention without undue experimentation.

(2) *The Amount Of Direction Or Guidance Presented*

The specification provides an ample disclosure of how to make and use the constructs of the invention. For example, on pages 3-7 and in the Examples 1 and 2 (pages 11-22) the specification teaches in details how to use claimed DNA constructs, the influence of different combinations of constructs, promoters and enhancers on the expression of an α-galactosidase gene, and how to transfer an α-galactosidase gene into a mouse model of Fabry's disease. Such an extensive disclosure provides a significant guidance to a skilled artisan of how to make and use the claimed invention without undue experimentation, as all of the elements of the claimed method and composition are described in great detail.

(3) *The Presence Of Working Examples*

The specification provides a full description of how the compositions of the invention were used by way of working examples. In particular, disclosed is a method of transfer of α-galactosidase gene into a Fabry-diseased mouse by way of intramuscular injection of a DNA construct that resulted in enhanced expression of human α-galactosidase in culture medium of

the pX3F-, pX4F- or pX7F-transfected myoblasts (see, *e.g.,* page 13, line 16 through page 14, line 7 of the specification). Also described are the effects of muscle-specific regulatory elements on the expression of human α-galactosidase (see, *e.g.,* Table 1 on page 12 of the specification) and its enhanced production after intramuscular injection of plasmid DNA (see, e.g., Example 1, pages 14-15 of the specification). It is noteworthy that these experiments were the first report in which a correctly glycosylated form of human α-galactosidase was expressed and secreted from differentiated muscle cells.

(4) *The Nature Of The Invention*

The invention is directed to a method for treatment of a metabolic disorder or condition related to an α-galactosidase A deficiency, and a pharmaceutical composition comprising an expression cassette used in the method of the invention.

(5) *The State Of The Art*

Gene transfer therapy of Fabry disease was known and appreciated by those skilled in the art at the time of the invention. Sugimoto and colleagues (Sugimoto *et al.*, "Retroviral Co-expression of Multidrug Resistance gene and Human Alpha-Galactosidase A for Gene Therapy of Fabry Disease", *Hum Gene Ther* 1995 (July), 6(7):905-915) reported on developing a retroviral vector system for carrying among others human alpha-galactosidase A genes capable of high level expression of the enzyme. The authors discussed the usefulness of these vectors in the gene therapy of Fabry disease. In a later publication (Sugimito *et al.*, "*In vivo* Drug-Selectable Markers in Gene Therapy", *Leukemia* 1997 (April), 11, Suppl 3:552-556), the authors demonstrated the co-expression of human multidrug resistance gene with alpha-galactosidase A as a model for gene therapy of Fabry disease. The other group of researchers (Ohshima *et al.*, "Alpha-Galactosidase A Deficient Mice: A Model of Fabry Disease", *PNAS* USA, 1997 (March), 94:2540-2544) demonstrated the correction of embryonic alpha-galactosidase A deficient fibroblasts by transducing these cells with bicistronic multidrug resistance retroviruses containing alpha-galactosidase A cDNA. "Because an enabling disclosure by definition turns upon the objective understanding of a skilled artisan, the enablement requirement can be met by reference to the knowledge of one of ordinary skill in the relevant art." *See*, MPEP § 2321, § 2340. Additionally, it is respectfully submitted that the post-filing publications, for example, those referred to in the previous response filed October 2, 2006 (for example, U.S. Patent No. 6,066,626, Jung *et al.*, *PNAS* USA 98(5):2676-2681 (2001), Qin *et al.*, *PNAS* USA 98(6):3428-3433 (2001), *etc.*) can be viewed as evidence that the teachings of the instant application do work.

(6) *The Relative Skill Of Those In The Art*

The relative skill of those in the pertinent art is high. As the specification provide a sufficient disclosure of all the elements of the claims and the state of the art reveals that the knowledge of gene transfer therapy of Fabry disease existed at the time the invention was made, it is respectfully submitted that a skilled artisan would be able to make and use the invention without undue experimentation based on the instant disclosure and knowledge available at the time of the invention. "The purpose of the enablement provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and the knowledge in the art." *See*, MPEP § 2140.

(7) *The Predictability Or Unpredictability Of The Art*

The pertinent art is highly unpredictable. Nevertheless, the amount of guidance and the working examples provided in the instant specification are sufficient to enable a skilled artisan to make and use the invention without undue experimentation (as discussed in items 1 to 6 above).

(8) *The Breadth Of The Claims*

Claims are drawn to a method for treatment of a metabolic disorder or condition related to an α-galactosidase A deficiency and a pharmaceutical composition to be used in the claimed method. It is respectfully submitted that all the elements of the claimed method and composition are disclosed in the specification and the examples in great detail including the expression cassette, the myosin enhancers, the promoters, the polynucleotide sequences of interest, the vectors, the DNA constructs and how to make and use them in the method as claimed (see, e.g., pages 3-7 of the disclosure). Therefore, the disclosure is fully enabling to a skilled artisan to make and use the instant invention without undue experimentation and commensurate in scope with the breadth of the claims.

Thus, it is respectfully requested that the rejection of claims 31-35, 40-42, 51 and 97-99 under 35 U.S.C. §112, first paragraph, be withdrawn. Claims 58-62, 67-69 and 78 are cancelled rendering the rejection moot with respect to these claims. Accordingly, the rejection under 35 U.S.C. 112, first paragraph, enablement, should be withdrawn.

V. INFORMATION DISCLOSURE STATEMENT

Applicant submits herewith a supplemental Information Disclosure Statement and PTO Form 1449 citing the references listed in the instant specification on pages 24 and 25 that were

not cited in the Information Disclosure Statement filed in the above-referenced case on July 31, 2002. A copy of the initialed Form 1449 filed on July 31, 2002 and considered by the Examiner on October 27, 2004 is attached hereto as evidence of a proper submission on July 31, 2002.

CONCLUSION

In light of the above amendments and remarks, Applicant respectfully submits that claims 31-35, 40-42, 51 and 97-99 satisfy all the criteria for patentability and requests to consider the subject application towards allowance.

No fees other than the extension of time fees are believed to be due. However, the Commissioner is hereby authorized to charge any required fee(s) to Jones Day Deposit Account No. 50-3013 (referencing the Attorney Docket No. 10103-004-999).

Respectfully submitted,

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by: Irina E. Britva, Ph.D., Patent Agent Reg. No. 50,498
for: Anthony M. Insogna Reg. No. 35,203

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939